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(54) Pharmaceutical compositions.

(57) The present invention provides a pharmaceutical composition for the transdermal systemic administration of an active agent characterised in that the active agent is bopindolol or methysergide. Also the present invention provides a pharmaceutical composition for the transdermal systemic administration of a pharmacologically active agent characterised in that it contains bopindolol, tizanidine, clemastine, ketotifen or methysergide as active agent in a reservoir comprising a hydrophilic polymer. Furthermore a pharmaceutical composition for the transdermal systemic administration of pharmacologically active agents characterised in that the pharmacologically active agent is in a reservoir comprising a polyacrylate polymer containing cationic ester groups.

EP 0 315 217 A2



DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
X	DE-A-2 902 183 (RINGWELSKI et al.) * Page 9, line 4 - page 10, line 1; page 10, lines 15-20; page 10, line 35 - page 11, line 5; figures *	1,3	A 61 M 37/00 A 61 M 35/00
Y		6-8	
P,X	FR-A-2 562 800 (LABORATORIES FOURNIER) * Page 4, line 31 - page 5, line 12; page 6, lines 27,28; figure 1; page 3, lines 1-5 *	1,3-5	
A	GB-A- 845 841 (F. MEYER). * Page 3, lines 75-80,106-115,22-26; figure 3 *	1,3-5	TECHNICAL FIELDS SEARCHED (Int. Cl.4)
A	GB-A-2 093 694 (CAMPBELL et al.) * Page 3, lines 41-48; page 3, line 126 - page 4, line 2 *	2,3,5	A 61 M
A	US-A-4 486 193 (SHAW & GALE) * Column 4, lines 55-66 *	3	
Y	EP-A-0 114 125 (ALLISON et al.) * Figures 2,4; page 6, lines 21-24; page 7, lines 25-29 *	6-8	
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 25-09-1986	Examiner RAKOWICZ, J.M.
CATEGORY OF CITED DOCUMENTS			
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document	

transdermally from a drug reservoir comprising a hydrophilic polymer having the pharmacologically active agent dispersed throughout.

Tizanidine, ketotifen and clemastine have previously been disclosed for transdermal administration. GB 2098865 A discloses topical microemulsions containing these pharmacologically active agents. The microemulsions are to be applied to the skin as a cream.

Tizanidine is a known myotonolytic agent e.g. for the treatment of local muscle spasms e.g. rheumatic pains and spastic conditions. Ketotifen and clemastine are anti-histamines e.g. for the treatment of allergic conditions. Ketotifen also is an anti-anaphylatic agent, e.g. for the prophylaxis of asthma.

In a further aspect the present invention provides a pharmaceutical composition for the transdermal systemic administration of pharmacologically active agents characterised in that it contains bopindolol, tizanidine, clemastine, ketotifen or methysergide in a reservoir comprising a hydrophilic polymer. In yet a further aspect the present invention provides the use of these active agents in a hydrophilic polymer for the manufacture of a transdermal medicament suitable for systemic administration of the active agent through intact skin.

The hydrophilic polymers take up water and are permeable to water, e.g. moisture from the skin, although the polymers may be insoluble in water. The polymers may swell and provide release of a large amount of pharmacologically active agent leading to a high concentration gradient of pharmacologically active agent between the skin surface and stratum corneum at a pH of from 4 to 7, preferably at skin pH, e.g. 5.5. If desired they may be soluble in organic solvents. Examples of suitable polymers include polyacrylamide and its co-polymers, polyvinylpyrrolidone (PVP), vinyl acetate/vinyl alcohol co-polymers, polyvinyl alcohol (PVA) and derivatives, ethyl cellulose and other cellulose and starch derivatives.

The polymer preferably has a mean molecular weight of from about 50,000 to about 300,000 Daltons, such as 100,000 to 200,000 Daltons, and is preferably film forming.

Hydrophilic polyacrylates are preferred polymers. The acrylate may be substituted, e.g. a methacrylate. They may be commercially available acrylate/methacrylate co-polymers. Some or all of the acid groups may be esterified, e.g. with alkyl groups such as methyl or ethyl groups. Preferably at least 2% of the alkyl groups may contain polar substituents, e.g. a hydroxy group.

It has been found that polyacrylates containing cationic functional groups are especially preferred.

Transdermal pharmaceutical compositions for the systemic administration of pharmacologically active agents through intact skin wherein the active agent is in a reservoir comprising a polyacrylate containing cationic functional groups are novel and form part of the present invention.

The present invention also provides the use of a pharmacologically active agent in a polyacrylate containing cationic groups for the manufacture of a medicament suitable for transdermal systemic administration of the pharmacologically active agent through intact skin of a subject. In another aspect the present invention provides a method of systemically administering a pharmacologically active agent to a subject which comprises contacting a reservoir of the pharmacologically active agent in a polyacrylate containing cationic ester groups to intact skin.

Examples of cationic groups include dialkylaminoalkyl groups, e.g. dimethylaminoalkyl groups.

Especially preferred cationic groups include quaternary ammonium groups, preferably a tri(alkyl)-aminoalkyl group. Examples of such groups are trimethylaminoethyl ester groups.

The polyacrylate may contain some carboxylic acid groups in free form or salt anions, e.g. chloride anions in order to balance the cationic groups.

The ratio of cationic groups to neutral groups is preferably from 1:10 to 1:50 e.g. from 1:20 to 1:40.

Preferably the polymers have an alkali count (defined in analogous manner to acid count) of from about 10 to about 200 mg KOH per gram polymer, e.g. 10 to 30 mg KOH per gram polymer.

Examples of commercially available polymers of this type include:-

1) Polymers of acrylate and methacrylate esters containing methyl and ethyl neutral ester groups and trimethylaminoethyl cationic ester groups. Chloride ions are present. Mean Molecular weight 150000 Daltons. Viscosity (20°C), maximum 15cP. Refractive index 1.380 - 1.385. Density 0.815 - 0.835 g/cm³. Ratio of cationic ester groups to neutral alkyl groups 1:20 giving an alkali count of 28.1 mg KOH per gram polymer (Eudragit RL 100 Registered Trade Mark available from Röhm, Darmstadt, W.Germany) or 1:40 giving an alkali count of 15.2 mg KOH per gram polymer (Eudragit RS 100 Registered Trade Mark, also available from Röhm).

2) Polymer of methacrylate esters containing trimethylaminoethyl cationic ester groups and other neutral (C₁₋₄)alkyl ester groups. Chloride ions are present. Mean molecular weight 150,000. Viscosity (20°C), 10 cP. Refractive Index 1.38. Density 0.815. Alkali number of 180 mg KOH per gram polymer (Eudragit E 100, Registered Trade Mark, also available from Röhm).

The penetration of the active agent through isolated rat and human skin may be followed in the well known diffusion test effected according to the principles, e.g. set out in GB 2098865 A and in T.J.Franz, J.Invest.Dermatol (1975), 64, 191-195. The pharmaceutical compositions of the invention are applied to the external side of isolated rat or human skin pieces about 2 cm² in area. The rat skin is hairless. The other side is continuously washed with physiological saline. The amount of active agent in the saline is determined in conventional manner, e.g. HPLC. The penetration flux over 24 hours may then be ascertained, and if desired the steady state flux. The penetration flux rate is in the order of 1 to 10 micrograms/cm²/hour.

Alternatively the penetration of the active agent may be followed in vivo by applying the pharmaceutical composition to intact skin, e.g. on the chest, back, arm or behind the ear, of a subject and measuring the amount of active agent in the blood.

The pharmaceutical compositions of the invention may be used for the same indications as known for oral or intravenous administration. The amount of pharmaceutically active agent to be administered will individually depend on the drug release characteristics of the pharmaceutical compositions, the drug penetration rate observed in in vitro and in vivo tests, the potency of active agent, the size of the skin contact area, the part of the body to which the unit is stuck, and the duration of action required. The amount of active agent and area of the pharmaceutical composition etc may be determined by routine bioavailability tests comparing the blood levels of active agents after administration of the active agent in a pharmaceutical composition according to the invention to intact skin and blood levels of active agent observed after oral or intravenous administration of a therapeutically effective dose of the pharmacologically active agent.

Given the daily dose of a drug for oral administration, the choice of a suitable quantity of drug to be incorporated in a transdermal composition according to the invention will depend upon the pharmacokinetic properties of the active agent, including the first pass effect; the amount of drug which can be absorbed through the skin from the matrix in question for a given area of application and in a given time; and the time for which the composition is to be applied. Thus, a drug with a high first pass effect may require a relatively low quantity in the transdermal composition when compared with the oral daily dose, since the first pass effect will be avoided. On the other hand, generally a maximum of only approx. 50% of the drug in the matrix is released through the skin in a 3 day period.

The pharmaceutical compositions of the invention in general have for example an effective contact area of drug reservoir on the skin of from about 1 to about 50 square centimetres, preferably about 2 to 20 square centimetres, and are intended to be applied for from 1-7 days, preferably 1-3 days.

Examples of representative doses are:-

1) Tizanidine A dose of 20 mg in a patch of ca 10 cm² to be administered once every 3 days for the systemic treatment of rheumatic pains and muscle spasms.

2) Bopindolol A dose of 1 to 10 mg in a patch of 10 cm² to be administered once over 3 consecutive days in each week for treatment of hypertension.

3) Clemastine A dose of about 1 to 20 mg in a patch of ca 10cm² to be administered once every 3 days for treatment of allergies, e.g. hay fever.

4) Ketotifen A dose of about 1 to 20 mg in a patch of ca 10cm² to be administered once every 3 days for prophylaxis of asthma.

5) Methysergide A dose of about 1 to 10 mg in a patch of ca 10 cm² to be administered once every 3 days for prophylaxis of migraine and migraine interval treatment.

The pharmaceutical compositions of the invention may be produced in conventional manner by dispersing or dissolving an appropriate pharmacologically active agent through a hydrophilic drug reservoir.

The weight ratio of pharmacologically active agent to hydrophilic polymer may vary between wide limits. The weight ratio may be for example sufficient to produce a supersaturation of the pharmacologically active agent in the drug reservoir. In general the weight ratio is from about 1:10 to about 1:1.

For example in the case of tizanidine the amount may be for example from 10 to 40 percent, e.g. 15 to 30 or 20 to 25 percent, by weight.

If the drug reservoir is not itself adhesive a pressure sensitive adhesive may be used to stick the drug reservoir to intact skin. Any conventional adhesive may be used, e.g. a polyacrylate. The layer may be applied to the drug reservoir and have a thickness of from about 1 to about 200 microns preferably 10 to 100 microns. If the adhesive layer is thin enough then the pharmacological agent will pass through it. Alternatively the adhesive layer may be applied to the edges of an outer cover for the drug reservoir and the outer cover stuck to the intact skin holding the drug reservoir in close contact with the intact skin.

The drug reservoir may be produced in conventional manner, e.g. in an adhesive plaster or patch. If it is a polymer matrix it may be produced by dispersing or dissolving the pharmacologically active agent in a

matrix as a thin layer (0.1 mm thickness) in analogous manner.

The aluminium foil is then cut up into patches about 10 sq cm in area.

Unless otherwise stated the drug matrix is built up from one film layer. It may if desired be built up as more than one layer.

- 5 The release of active agent is measured in vitro in standard skin diffusion tests through freshly isolated hairless rat skin. The rat skin piece is located in a Franz diffusion chamber - see T.J.Franz, J.Invest.Dermatol 1975 (64) 191-195. The receptor phase is pumped continuously and every hour samples are taken and measured for active agent content using HPLC. The trial lasts 24 hours and the penetration flux over 24 hours (hereinafter referred to as "flux") and if desired a steady state flux after a lag time of 3 to
10 10 hours is measured.

EXAMPLE 1: Tizanidine composition

- 15 Prepared as disclosed in Example A with a composition of
Tizanidine hydrochloride 20%
PAM Amine Polymer RL 40%
Polyoxyethylene-10 oleyl ether 40%
Active agent penetration rate in rat skin:
20 Penetration Flux \pm = 0.0145 mg/cm²/hr
Total penetration \pm = 0.290 mg/cm² ca 21.46%
Remainder detected in plaster ca 47%

25 EXAMPLE 2: Tizanidine composition

- Prepared in analogous manner to that described in Example A with a composition of
Tizanidine hydrochloride 1.144 g
PAM Amine polymer RL 1.928 g
30 Polyoxyethylene-10 oleyl ether 1.928 g
The active agent is dissolved in 5 g ethanol as solvent.
Spreading speed 6 mm/sec.
Thickness of wet film 0.25 mm.
Concentration of active agent in film 2.6 mg/cm²
35 No adhesive acrylate film is present.
Active agent penetration rate through rat skin:
Penetration Flux = 8.5 microgram/cm²/hr
Steady state flux = 16.2 microgram/cm²/hr
In a clinical trial a 2 cm² patch of the composition is applied to the left underarm and after 12, 24 and
40 36 hours the remaining tizanidine content in the patch determined.
Flux rate = 5.1 microgram/cm²/hr

EXAMPLE 3:

- 45 Prepared as described in Example 2 using a solvent methylene chloride instead of ethanol. Composition:

50	Tizanidine hydrochloride	1.144 g
	PAM Amine polymer RL	1.928 g
	Polyoxyethylene-10 oleyl ether	1.628 g
	Triacetin (1,2,3)	0.250 g

- 55 Penetration rate through rat skin:
Penetration Flux 10.4 microgram/cm²/hr
In a clinical trial a 2 cm² patch was applied as in Example 2.
Penetration Flux 4.9 microgram/cm²/hr

Example	9	10	11	12
Bopindolol hydrogen malonate	1.275 g	1.275 g	-	-
Bopindolol free base	-	-	1.0 g	1.0 g
PAM Amine polymer RL	1.225 g	1.225 g	-	-
PM Amine polymer E	-	-	2.665 g	2.665 g
Polyoxyethylene-(10) oleyl ether	-	0.25 g	1.335 g	-
Polyethylene-(9) glycol glyceryl cocoate	-	-	-	1.335 g
Azone	2.5	2.25 g	-	-
Solvent	CH ₂ Cl ₂	CH ₂ Cl ₂	CH ₃ OH	CH ₃ OH
Solvent amount (g/g dry film)	1.0	1.0	4.0	4.0
Thickness of wet film (mm)	0.25	0.25	0.3	0.3
Spreading speed (mm/sec)	6	6	6	6
Acrylate adhesive film (Wet film thickness)	None	None	None	None
Active Agent Penetration through isolated rat skin.				
Penetration Flux (microgram/cm ² /hr)	1.7	4.0	11.1	8.6
Steady Rate flux (microgram/cm ² /hr)	5.7	12.5	59.0	33.0

EXAMPLE 13 - 16: Ketotifen pharmaceutical compositions

The following compositions are made in analogous manner to Example 2.

Example	13	14	15	16
Ketotifen hydrogen fumarate	0.5 g	0.5 g	-	-
Ketotifen free base	-	-	1.0 g	1.0 g
PAM Amine Polymer RL	-	-	2.0 g	2.0 g
PM Amine Polymer E	2.5 g	2.5 g	-	-
Polyoxyethylene (20) sorbitan monooleate	-	-	-	2.0 g
Polyethylene glycol 300	-	2.0 g	-	-
Polyethylene glycol-(7) glyceryl cocoate	2.0 g	-	2.0 g	-
Solvent	Acetone	Acetone	Acetone	Acetone
Thickness of wet film (mm)	0.2	0.2	0.2	0.2
Spreading speed (mm/sec)	6	6	6	6
Acrylate adhesive film	None	None	None	None
Active Agent Penetration through isolated rat skin	6.8	8.5	4.0	2.8
Penetration Flux (microgram/cm ² /hr)				
Steady state flux (microgram/cm ² /hr)	10.0	15.0	18.0	12.0

EXAMPLE B:

In analogous manner to that described in Example A a pharmaceutical composition is made without an acrylate adhesive layer. The drug matrix is based on an elastomer.

7. A pharmaceutical composition according to any one of claims 1 to 6 substantially as hereinbefore described with reference to any one of the examples.

8. A process for the production of a pharmaceutical composition for transdermal administration which comprises dispersing a) ketotifen in a polyacrylate polymer containing cationic ester groups, to form a drug
s reservoir, b) ketotifen through a hydrophilic polymer and optionally applying an adhesive layer.

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- 1 Wirkstofffreisetzungsrates und insbesondere auch die gewünschte lange
Zeitdauer der Wirkstofffreisetzung bei einer noch akzeptablen Pflaster-
größe zu erzielen.
- 5 Arbeitet man eine größere Wirkstoffmenge in ein solches Pflaster ein
als dem Sorptionsvermögen der filmbildenden Pflasterbestandteile
entspricht, so muß der Wirkstoff möglichst fein bis amorph in der
Klebermatrix verteilt sein, um durch rasches Nachlösen über die
Applikationsdauer den Sättigungszustand des Haftklebers weitmöglichst
10 aufrecht zu erhalten und auf diese Weise den Grad der Abnahme der
Geschwindigkeit der Freisetzung des Wirkstoffes aus dem Pflaster so
klein wie möglich zu halten. Eine Möglichkeit in Bezug auf die
geläufigen Ausstreichverfahren zur Herstellung von Pflasterfilmen
besteht darin, Filmbildner und Wirkstoff gemeinsam in einem organi-
15 schen Lösungsmittel zu lösen, die Lösung bis zur streichfähigen
Viskosität einzuengen und die wirkstoffhaltige Kleberlösung dann
auf großflächige Bahnen auszustreichen und zu trocknen. Dieses
Verfahren führt jedoch bei leicht flüchtigen, flüssigen oder kristal-
linen Wirkstoffen für die bei Kautschuk-Pflasterfilmen üblichen
20 Kleberformulierungen zu Stabilitätsproblemen, bedingt durch Nach-
kristallisations- und Verdunstungsprozesse, die zu einer unkontrol-
lierten, unreproduzierbaren Wirkstofffreisetzung und Verschlechterung
der Klebeeigenschaften führen.
- 25 Die galenische Entwicklung von Wirkstoffpflastern dieser Art gestaltet
sich darüberhinaus in der Praxis dadurch besonders schwierig, daß die
Pflasterrezeptur sowohl bezüglich ihrer Klebeeigenschaften als auch
bezüglich ihrer Durchlässigkeit für den oder die eingearbeiteten
Wirkstoff bzw. Wirkstoffe zu optimieren ist.
- 30 Aufgabe der vorliegenden Erfindung ist es daher, die vorgenannten
Nachteile bisheriger Wirkstoffpflaster, insbesondere auf dem Gebiet
der Betablocker, Steroidhormone, Calciumantagonisten und herzwirksamen
Wirkstoffen wie Bupranolol, Propranolol, Estradiol, Nitroglycerin
oder Isosorbitdinitrat, sowohl im Hinblick auf ihre Wirkstofffreisetzung
35 als auch ihre Herstellung bzw. Entwicklung zu überwinden und ein

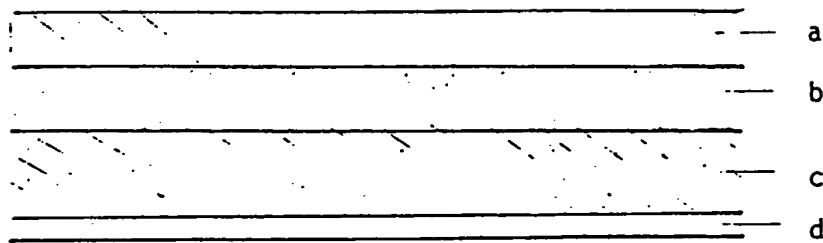


Figure 1

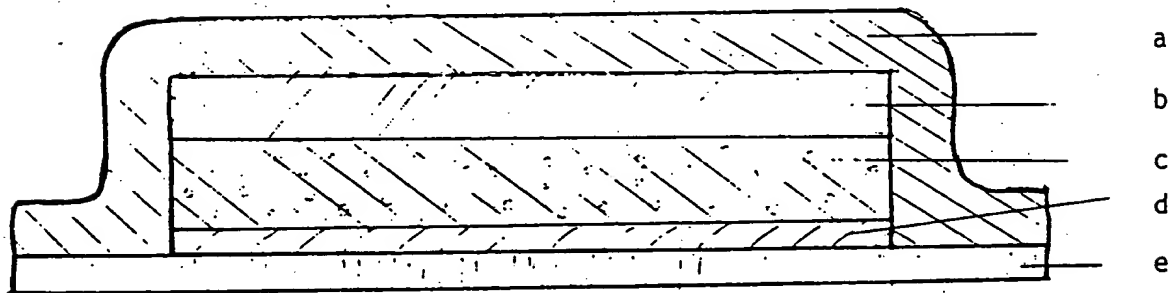


Figure 2

1 der Klebmasse befindlichen Wirkstoffanteile und/oder eine Erhöhung
der Viskosität der bei der Fertigung der erfindungsgemäßen Wirkstoff-
pflaster verwendeten Kleberlösung sowie eine Verbesserung der Kohärenz
und Hafteigenschaften des Klebefilms erreicht.

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Beispiele für die im erfindungsgemäßen Wirkstoffpflaster in der
Kautschuk/Klebeharzmasse zugesetzten, in Wasser quellfähigen Poly-
meren sind Produkte wie Galaktomannane, Celluloseprodukte, Tragant,
Polyglycoside, Polyvinylpyrrolidone, feinpulverisierte Polyamide,
10 wasserlösliches Polyacrylamid, Carboxyvinylpolymerisate, agar-ähnliche
Algenprodukte, Mischpolymerisate aus Methylvinyläther und Malein-
säureanhydrid, Guar-Gummi, Typen wie Hydroxypropylguar-Gummi oder
Guar-Mehl, Gummi arabicum, Dextrin und Dextran, mikrobiologisch
gewonnenes Polysaccharid-Gummi wie das Polysaccharid B 1459 oder
15 die gut wasserlösliche Type Keltrol bzw. synthetisch gewonnene
Polysaccharide wie das Produkt Ficoll, Methylglucosederivate,
Hydroxymethylpropylcellulose, Polygalakturonsäurederivate wie
Pectin oder das amidierte Produkt Pectinamid.

20 Dabei sind besonders bevorzugt Galaktomannane, mikrokristalline
Cellulose und Tragant. Ganz besonders bevorzugt sind Galaktomannane
und Tragant für das Steroidhormon Estradiol, mikrokristalline Cellu-
lose für Bupranolol und Nitroglycerin.

25 Gemäß einer besonderen Ausführungsform der vorliegenden Erfindung
unterteilt sich der Klebefilm aus der Kautschuk/Klebeharzmasse
in eine einschichtige Wirkstoff- und das in Wasser quellbare Polymere
enthaltende Reservoirschicht aus der Kautschuk/Klebeharzmasse und
eine zur Schutzschicht hin liegende, gegebenenfalls Wirkstoff ent-
30 haltende Haftklebeschicht aus der Kautschuk/Klebeharzmasse und
befindet sich zwischen der Reservoirschicht und der Haftklebeschicht
eine Trennschicht, die für die Kautschuk/Klebeharzmasse und den
in ihr gelösten Wirkstoff vollständig, für das in Wasser quellbare
Polymere nicht oder nur teilweise durchlässig ist. Die Ausführungs-
35 form mit der Trennschicht ist bevorzugt, wenn der Klebefilm sich